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Study ID: CMO-MA-EYE-0590

Title: XEN 45 Gel Stent: Long Term Performance and Safety Assessment (XEN LT)

Protocol Date:17Sept2018

Retrospective Observational Study Protocol

Study No	CMO-MA-EYE-0590
ClinicalTrial.gov Registration Number	Not yet registered
Product	XEN® 45 Gel Stent
Product reference	██████████
Study Title	XEN 45 Gel Stent: Long Term Performance and Safety Assessment (XEN LT)
Clinical Phase	Post-market clinical follow-up study
Study Sponsor	Allergan Pharmaceuticals International Limited Clonshaugh Industrial Estate, Coolock, Dublin D17 E400, Ireland
Date of Protocol	17 Sep 2018
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Table of contents

Table of contents.....	2
List of Tables.....	5
List of Figures	5
1 SYNOPSIS.....	6
2 LIST OF ABBREVIATIONS	11
3 Study Milestones and Timelines.....	12
4 Amendments and Updates	13
5 INTRODUCTION	13
5.1 Background	13
5.2 Study Rationale	14
6 OBJECTIVES AND OUTCOME VARIABLES.....	15
6.1 Objectives	15
6.1.1 Primary objective.....	15
6.1.2 Secondary objective.....	15
6.2 Key Variable Definitions	15
6.3 Outcome Variables	15
7 STUDY CONDUCT	17
7.1 Overall Design of the Study	17
7.2 Data Collection Periods	18
7.3 Patient Discontinuation, Site Termination or Study Termination	19
7.3.1 Withdrawal of Individual Patients Prior to Study Completion.....	19
7.3.2 Study or Study Site Termination	19
8 STUDY POPULATION	19
8.1 Sites	19
8.2 Patients	20
8.2.1 Inclusion Criteria	20
8.2.2 Exclusion Criteria.....	20
8.2.3 Minimum Required Dataset	20
9 STUDY PROCEDURES	21
9.1 Site Selection, Enrollment and Training.....	21
9.1.1 Sampling.....	21
9.1.2 Site Initiation	21

9.1.3	Site Monitoring	21
9.2	Patient Identification and Selection Procedures	22
10	STUDY ASSESSMENTS	23
10.1	Data Collected in the Screening Log	23
10.2	Demographics	23
10.3	Ocular and Glaucoma Medical History.....	23
10.4	Surgery-Related Data	23
10.5	Intraocular Pressure Data	24
10.6	Eye Assessments	24
10.6.1	Visual Field Exam	24
10.6.2	Best Corrected Visual Acuity.....	24
10.7	Needling Procedures	24
10.8	Secondary Surgical Intervention	24
10.9	Safety Assessments.....	24
10.9.1	Definitions	24
10.9.2	Collection and reporting of Safety Events by Investigators	25
10.9.3	Case Processing and Submission to Competent Authorities	26
11	DATA SOURCES	26
12	DATA MANAGEMENT	27
13	QUALITY CONTROL	27
14	STATISTICAL METHODS	28
14.1	Sample Size	28
14.2	Study Populations and Analyses	28
14.2.1	Study Populations and Analysis Methods	28
14.2.2	Disposition and Patients' characteristics	29
14.2.3	Disease Progression	29
14.2.4	Primary Objective	29
14.2.5	Secondary Objectives	29
14.2.5.1	<i>Change in IOP and Number of Topical IOP-Lowering Medications 4 Years after XEN 45 Gel Stent Implantation.....</i>	<i>29</i>
14.2.5.2	<i>Success over the Long Term of following implantation of the XEN 45 Gel Stent</i>	<i>29</i>
14.2.5.3	<i>Safety over the long term following implantation of the XEN 45 Gel Stent.....</i>	<i>29</i>

14.3 Bias and Limitations of the Study	30
14.3.1 Sites.....	30
14.3.2 Patients.....	30
14.3.3 Information Bias.....	30
15 ETHICAL CONDUCT OF THE STUDY.....	31
15.1 Ethics Statement	31
15.2 Informed Consent	31
15.3 Institutional Review Board / Independent Ethics Committee Approval.....	31
15.4 Adherence to the Protocol	31
15.5 Protocol Amendment	31
15.6 Retention of Patient Records	32
15.7 Confidentiality	32
16 Plans for disseminating and communicating study report	32
17 REFERENCES	33
APPENDICES	35

List of Tables

Table 1	Study Milestones and Timelines	12
Table 2	Schedule of Data Collection	19
Table 3	Data Collected in Screening Logs	23
Table 4	Result from the MS-001 Study	28

List of Figures

Figure 1	Examples of Data Extraction Period for Eligible Eyes	18
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1 SYNOPSIS

Title	XEN 45 Gel Stent: Long Term Performance and Safety Assessment (XEN LT)
Protocol number	CMO-MA-EYE-0590
Clinical trials.gov Registration Number	Not yet registered
Planned study dates	Data extraction is planned to be conducted between fourth quarter 2018 and second quarter 2019.
Objectives	<p>Primary objective:</p> <ul style="list-style-type: none"> The primary objective of this study is to assess the performance of XEN 45 Gel Stent over the long term as assessed by the change in intraocular pressure (IOP) compared to medicated IOP at baseline and the change in the number of topical IOP-lowering medications compared to baseline, 3 years after implantation. <p>Secondary objectives:</p> <ul style="list-style-type: none"> Assess the performance of XEN 45 Gel Stent over the long term as assessed by the change in IOP compared to medicated IOP at baseline and the change in the number of topical IOP-lowering medications compared to baseline, 4 years after implantation. Assess success over the long term following implantation of the XEN 45 Gel Stent^[a]. Assess safety over the long term following implantation of the XEN 45 Gel Stent <p>[a] <i>Qualified success</i> of implantation of the XEN 45 Gel Stent will be defined as $\geq 20\%$ reduction from medicated baseline with no secondary surgical intervention (SSI) for glaucoma and no clinical hypotony (as defined in synopsis section "Data Collection and Procedures") while staying on same or fewer topical IOP-lowering medications than at baseline.</p> <p><i>Complete success</i> of implantation of the XEN 45 Gel Stent will be defined as $\geq 20\%$ reduction from medicated baseline with no SSI for glaucoma and no clinical hypotony while taking no topical IOP-lowering medications.</p>
Study Design	This is a retrospective, non-interventional, observational, multi-center, chart review study to be conducted in patients who underwent placement of the XEN 45 Gel Stent as a standalone procedure or in combination with phacoemulsification from 1 January 2014 to 1 October 2015.
Rationale	XEN 45 Gel Stent performance and safety have been previously demonstrated in clinical trials designed for regulatory approval. However, studies conducted to date only provide data up to 2 years. This study will allow an assessment of the long-term performance and safety of the XEN 45 Gel Stent surgeries performed in Europe in typical clinical settings.

Duration of study	<p>Data extraction will cover the period from 1 January 2014 up to 1 October 2018.</p> <p>For each eye selected, retrospective data available from baseline (i.e., day when decision was made to implant XEN 45 Gel Stent) until Last Visit (i.e., date of the last follow-up visit available prior to 1 October 2018 or date on which the patient had a SSI for glaucoma, whichever occurs first), will be extracted from existing medical records.</p>
Patient Population and Key Selection Criteria	<p>The study population will include eyes treated with XEN 45 Gel Stent for open angle glaucoma as a standalone procedure or in combination with phacoemulsification between 1 January 2014 and 1 October 2015; and with documented post-operative follow-up available in the medical charts. For patients implanted bilaterally both eyes can be entered into the study database if they both meet eligibility criteria.</p>
Sample Size	<p>This chart review study plans to accrue a minimum of 60 study eyes that have had at least 3 years of follow-up data after the initial implant with XEN 45 Gel Stent without a SSI for glaucoma. Based on data from the MS-001 trial, it has been assumed that mean IOP reduction at 3 years will be -5.6 (± 6.32) mmHg. The 95% confidence interval (CI) of the projected mean reduction afforded by a sample of 60 study eyes is -7.2 to -4.0 mmHg. That is, the half-length of the interval is 1.6 mmHg, which provides a reasonable precision for the estimate of the projected mean reduction in IOP.</p> <p>Data collection for a study eye will stop at the Last Visit. While a precise sample size cannot be calculated, it has been assumed based on the 2-year outcomes from the MS-001 trial that selecting at least 150 eyes into the study will ensure that this chart review study will accrue a minimum of 60 study eyes with at least 3 years of follow-up data after the initial implant with XEN 45 Gel Stent.</p>
Outcome Variables and Assessments	<p>Performance</p> <ul style="list-style-type: none"> • Change in IOP from medicated baseline to 3 years after XEN 45 Gel Stent implantation • Change in IOP from medicated baseline to 4 years after XEN 45 Gel Stent implantation • Study pre-defined IOP outcomes achieved while staying on the same number or fewer IOP-lowering medications and without clinical hypotony: 20% reduction from medicated baseline, IOP below 12 mmHg, below 13 mmHg, ..., up to IOP below 18 mmHg • Change in the number of topical IOP-lowering medications from medicated baseline to 3 years after XEN 45 Gel Stent implantation • Change in the number of topical IOP-lowering medications from medicated baseline to 4 years after XEN 45 Gel Stent implantation • Qualified or complete success 3 years after XEN 45 Gel Stent implantation • Qualified or complete success 4 years after XEN 45 Gel Stent implantation

	<p>Safety</p> <ul style="list-style-type: none"> Adverse events of special interest (AESIs) as defined below in the Section "Data Collection Procedures"
Study Procedures	<p>Patients' medical charts will be extracted until the study target population has been reached. Site personnel will be required to complete a screening log for patients treated with XEN 45 Gel Stent on or after 1 January 2014 until 31 December 2014 to identify eligible patients. End date can be up to 1 October 2015 if the target number of eyes for the primary analysis has not been reached. For each eye selected, retrospective data will be extracted from existing medical records from XEN 45 Gel Stent implantation until 1 October 2018 or until the date on which the patient received a SSI for glaucoma, whichever occurs first. The study will not impose any separate patient visits at the site. In case key data are not available within the charts at the site, site personnel will be asked to liaise with the patients' treating ophthalmologist to request data to be made available for investigators for data entry.</p> <p>When both eyes from the same patient meet eligibility criteria, each eye will be included in the study database with a unique identifier, and eyes will be paired in the electronic data capture system.</p>
Data Collection Procedures	<p>Screening Log</p> <p>The following data concerning eyes treated at the site with XEN 45 Gel Stent during the period of interest will be extracted in anonymous screening logs. If both eyes of a patient had undergone XEN 45 Gel Stent implantation, one line should be completed in the screening log per treated eye.</p> <ul style="list-style-type: none"> Eye in which XEN 45 Gel Stent was implanted (Oculus Dexter vs. Oculus Sinister) Indication for XEN 45 Gel Stent implantation Date (MM YYYY) of XEN 45 Gel Stent implantation Date (MM YYYY) of Last Visit Reason why the patient has not been selected for the study, if applicable <p>Case Report Form</p> <p>The following data concerning eye treatment and clinical condition will be collected chronologically for eligible eyes at the indicated time points.</p> <p>Baseline is defined as the day when the decision was made to implant XEN 45 Gel Stent. For each selected eye, all retrospective data available from baseline until Last Visit, will be extracted from existing medical records.</p> <ul style="list-style-type: none"> Demographics at baseline (age, race and gender) <ul style="list-style-type: none"> Ocular and glaucoma medical history: glaucoma diagnosis and stage, previous ocular and glaucoma procedures, previous ocular medications (including whether or not eye is treated with Diamox on

	<p>the day when decision was taken to implant XEN 45 Gel Stent) and ocular pathologies observed at baseline.</p> <ul style="list-style-type: none"> • Surgery data: anti-metabolite and/or anti-fibrotic used prior to XEN 45 Gel Stent implantation, procedure performed (i.e., XEN 45 Gel Stent implantation alone or phacoemulsification + XEN 45 Gel Stent implantation), XEN 45 Gel Stent and cataract-related complications, and if available surgical notes • IOP data: IOP and number of IOP-lowering medications at baseline and at all data collection points defined for the study period. • Eye assessment: visual field exam and best corrected visual acuity at all data collection points defined for the study period. • Dates of needling procedures • SSI for glaucoma: nature and date • AESIs: <ul style="list-style-type: none"> ○ Anterior chamber defects (shallow with peripheral iridocorneal touch; flat with irido-corneal touch extending to the pupil); ○ Bleb leak; ○ Blebitis; ○ Choroidal effusion, hemorrhage or mixed effusion hemorrhage (extending posterior to the equator, with or without blood; obscuring disc or macula, with or without blood; with choroids touching in the center of the eye, with or without blood); ○ Corneal decompensation (transient i.e. <30 days or persistent i.e. >30days); ○ Endophthalmitis; ○ Hyphema (≥ 2 mm in height (layered) at any time; present or arising > 30 days postoperatively); ○ Persistent Hypotony (IOP < 6 mmHg, present at two consecutive visits postoperatively > 30 days apart); ○ Clinical Hypotony (vision reduction (2 lines or more) related to macular changes consistent with hypotony maculopathy (macular folds), optic disc edema, and/or serious choroidal detachments because of low IOP ○ Implant blockage; ○ Implant exposure or extrusion / conjunctival erosion; ○ Implant migration; ○ Implant repositioning requiring surgical intervention; ○ Implant touching iris or cornea; ○ Iritis (requiring treatment after the postoperative medication taper); ○ Macular edema; ○ Retinal detachment; ○ Suture abscess or other local infection; ○ Vitreous hemorrhage;
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	<ul style="list-style-type: none"> ○ And any other adverse event that leads to permanent visual impairment or requires surgical or medical intervention to prevent permanent visual impairment
Statistical Methods	<p>Analysis Populations</p> <p>Data will be presented for all eyes selected and meeting the selection criteria, i.e. Analysis Population. Additional groups may be also examined, as deemed appropriate (e.g. eyes that did or did not undergo phacoemulsification).</p> <p>Primary Objective</p> <p>Change in IOP from medicated baseline and change in the number of topical IOP-lowering medications compared to baseline will be summarized descriptively at Year 3 after XEN 45 Gel Stent implantation in eyes from the Analysis Population with at least 3 years of follow-up data and were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.</p> <p>Secondary Objectives</p> <p><i>Change in IOP and Number of Topical IOP-Lowering Medications at 4 Years after XEN 45 Gel Stent Implantation</i></p> <p>Change in IOP from medicated baseline and change in the number of topical IOP-lowering medications compared to baseline will be summarized descriptively at Year 4 after XEN 45 Gel Stent implantation in eyes from the Analysis Population with at least 4 years of follow-up data and were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.</p> <p><i>Success over the Long Term of Implantation of the XEN 45 Gel Stent</i></p> <p>Number and proportion of eyes achieving a 20% reduction in IOP from medicated baseline, and number and proportion of eyes with an IOP <18 mmHg, IOP <17 mmHg, ..., down to IOP<12 mmHg will be described at all data collection time-points in eyes from the Analysis Population that did not underwent SSI for glaucoma, did not have clinical hypotony, and were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.</p> <p>The number and proportion of eyes achieving "success" at 3 and 4 years after XEN 45 Gel Stent implantation will be summarized descriptively. Analyses will be conducted in the Analysis Population. Kaplan-Meier analyses will be conducted to analyze time from initial procedure to SSI for glaucoma.</p> <p><i>Safety over the Long Term of Implantation of the XEN 45 Gel Stent</i></p> <p>Surgical complications and post-operative AESIs will be summarized descriptively using frequencies and percentages. Analyses will be performed in the Analysis Population.</p>

The study shall be conducted in compliance with the ethical principles arising from the Declaration of Helsinki revised in 2013, ISO-14155-2011, European and National laws in terms of data protection, and the Guidelines on Medical Devices: Post Market Follow-Up Studies- a Guide for Manufacturers and Notified Bodies (MEDDEV 2.12/2 rev 2).

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
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AE	Adverse event
AESI	Adverse event(s) of special interest
BCVA	Best corrected visual acuity
CI	Confidence interval
CRA	Clinical research associate(s)
CRO	Contract research organization
EC	Exclusion criteria
eCRF	Electronic case report form
EDC	Electronic data capture
EDTRS	Early Treatment Diabetic Retinopathy Study
IC	Inclusion criteria
IEC	Independent ethics committee
IOP	Intra-ocular pressure
ISO	International Organization for Standardization
LogMAR	Logarithm of Minimum Angle of Resolution
MEDDEV	European Medical Device Vigilance System
MedDRA	Medical dictionary for regulatory activities
MIGS	Minimally invasive glaucoma surgery
OD	Oculus dexter
OS	Oculus sinister
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SSI	Secondary surgical intervention
WHO	World Health Organization

3 STUDY MILESTONES AND TIMELINES

The planned study milestones and timelines are described in Table 1 below.

Table 1 Study Milestones and Timelines

Milestone	Estimated Date
Ethics submission	Third quarter 2018
Start of data collection	Fourth quarter 2018
End of data collection	Second quarter 2019
Final Report of study results	Third quarter 2019

4 AMENDMENTS AND UPDATES

This section is not applicable (original protocol).

5 INTRODUCTION

5.1 Background

The term “glaucoma” refers to a group of diseases that have in common a characteristic damage to the optic nerve with associated visual field loss. Glaucoma is the second leading cause of blindness worldwide; blindness from glaucoma is irreversible. Glaucoma can occur in all age groups including infants, but it is most common in elderly people (Glaucoma Panel, 2016). Other risk factors include race with estimated prevalence being six times higher for certain age groups in black American populations, a steepest increase in open-angle glaucoma with age in white populations compared to black American populations, and a higher incidence of primary angle-closure glaucoma in Asian populations compared to white patients (McMonnies, 2016). There are two major types of glaucoma, primary open-angle glaucoma and primary angle-closure glaucoma.

The goal in the treatment of glaucoma is to prevent further loss of functional vision and to avoid an adverse impact on the patient’s quality of life (Glaucoma Panel, 2016). Glaucoma is a chronic progressive disease that requires continuous long-term cooperation of the patient with the glaucoma management proposed by the doctor. Currently, the only approach proven to be efficient in preserving visual function is lowering intra-ocular pressure (IOP) (Heijl et al., 2002) as elevated IOP is recognized as the primary risk-factor for glaucoma. IOP is lowered using medications, laser therapy or incisional surgery. Medical treatment is usually initiated as a first step in most cases. However, non-adherence to treatments dosed daily is common in glaucoma and has been linked to poor outcomes in vision-related quality of life (Thompson et al., 2018). Laser therapy is generally efficient in the first few months after treatment initiation, but has been shown to lose efficiency in the long term (Wienreb et al., 1995). Incisional surgeries can be defined as an attempt to lower IOP by the surgical formation of an artificial drainage pathway from the anterior chamber to the subconjunctival space (Lewis et al., 2014). Although several techniques have been developed to provide subconjunctival drainage, too many short- and long-term complications are still associated with this surgery, as over-filtration results in hypotony and under-filtration due to scarring in surgical failure (Watson et al. 1990).

More recently, several medical devices have been developed to treat glaucoma. The term “Minimally invasive glaucoma surgery” (MIGS), defined in a joint meeting of the American Glaucoma Society and US Food and Drug Administration (Caprioli et al., 2015), refers to a group of devices that are significantly less invasive and offers a new perspective of IOP reduction with less risk, short operating times and rapid recovery. The three main approaches of IOP reduction by MIGS devices include increasing trabecular–Schlemm’s canal outflow (iStent, Hydrus Microstent), increasing uveoscleral outflow via uveoscleral pathways (CyPass Micro-Stent), or creating a subconjunctival drainage pathway (XEN 45 Gel Stent) (Richter et al., 2016).

XEN 45 Gel Stent (Allergan Inc.) is an *ab interno* gelatin stent implanted via a clear corneal incision without conjunctival incision and is the only available filtering micro-invasive glaucoma surgery device that allows the subconjunctival filtration. The stent is intended to be implanted in the angle and through the sclera, connecting the anterior chamber to the subconjunctival space. It is a tube with an inside diameter of approximately 45 µm, its outside diameter is approximately 150 µm,

and it is approximately 6 mm long in its dry state. The gelatin imparts hydrophilic properties that allow the tube to expand when hydrated by contact with aqueous fluid. This expansion of the outer diameter of the tube aids in keeping the gelatin stent in its intended location after surgical implantation. The implant is housed in a disposable preloaded handheld inserter designed specifically for surgical implantation. The XEN 45 Gel Stent is intended to reduce intraocular pressure in patients with primary open angle glaucoma where previous medical treatments have failed (XEN 45 Gel Stent direction for use). The performance and safety of XEN 45 Gel Stent has been previously demonstrated in a few clinical trials. IOP reduction one year after XEN 45 Gel Stent has been shown to vary between 23% and 41% (Galal et al., 2017; De Gregorio et al., 2017; Mansouri et al., 2018, Perez-torregrosa et al. 2016, Stalmans and Vera, 2017). In a larger retrospective study including 242 eyes, decrease in IOP one year after XEN 45 Gel Stent implantation reached 54.1% (Hengerer et al., 2017) with a reduction in the number of IOP medication from approximately 3 before XEN 45 implantation to 0.3 one year after stent implantation. One prospective, multi-center, open-label trial, the MS-001 Trial, collected data over the 2 years following XEN 45 Gel Stent implantation (data not yet available). Overall, these studies demonstrated a good safety profile of XEN 45 Gel Stent with a relatively low number of events. Most common complications that may occur in conjunction with the use of XEN 45 Gel Stent include, but are not limited to, choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention (SSI) and other known complications of intraocular surgeries (e.g. flat or shallow chamber, corneal edema, endophthalmitis) (XEN 45 Gel Stent label).

5.2 Study Rationale

XEN 45 Gel Stent performance and safety have been previously demonstrated in clinical trials designed for regulatory approval. However, studies conducted to date only provide data up to 2 years. This study will allow an assessment of the long-term performance and safety of the XEN 45 Gel Stent surgeries performed in Europe in typical clinical settings.

6 OBJECTIVES AND OUTCOME VARIABLES

6.1 Objectives

6.1.1 Primary objective

The primary objective of this study is to assess the performance of XEN 45 Gel Stent over the long term as assessed by the change in IOP compared to medicated IOP at baseline and the change in the number of topical IOP-lowering medications compared to baseline, 3 years after implantation.

6.1.2 Secondary objective

The secondary objectives of this study are to:

- Assess the performance of XEN 45 Gel Stent over the long term as assessed by the change in IOP compared to medicated IOP at baseline and the change in the number of topical IOP-lowering medications compared to baseline, 4 years after implantation.
- Assess success over the long term following implantation of the XEN 45 Gel Stent as defined in Section 6.2.
- Assess safety over the long term following implantation of the XEN 45 Gel Stent.

6.2 Key Variable Definitions

Qualified success of implantation of the XEN 45 Gel Stent will be defined as $\geq 20\%$ reduction from medicated baseline with no SSI for glaucoma and no clinical hypotony while staying on the same number or fewer topical IOP-lowering medications than at baseline.

Complete success of implantation of the XEN 45 Gel Stent will be defined as $\geq 20\%$ reduction from medicated baseline with no SSI for glaucoma and no clinical hypotony while taking no topical IOP-lowering medications.

6.3 Outcome Variables

Performance outcomes:

- Change in IOP from medicated baseline to 3 years after XEN 45 Gel Stent implantation
- Change in IOP from medicated baseline to 4 years after XEN 45 Gel Stent implantation
- Study pre-defined IOP outcomes achieved while staying on the same number or fewer topical IOP-lowering medications and without clinical hypotony: 20% reduction from medicated baseline, IOP below 12 mmHg, IOP below 13 mmHg, ..., up to IOP below 18 mmHg
- Change in the number of topical IOP-lowering medications from medicated baseline to 3 years after XEN 45 Gel Stent implantation
- Change in the number of topical IOP-lowering medications from medicated baseline to 4 years after XEN 45 Gel Stent implantation
- Qualified or complete success 3 years after XEN 45 Gel Stent implantation

- Qualified or complete success 4 years after XEN 45 Gel Stent implantation

Safety outcomes:

- Adverse events of special interest (AESIs), as defined in Section 10.9.2.

7 STUDY CONDUCT

7.1 Overall Design of the Study

This is a retrospective, non-interventional, observational, multi-center, chart review study to be conducted in patients who underwent placement of the XEN 45 Gel Stent as a standalone procedure or in combination with phacoemulsification from 1 January 2014 to 1 October 2015. For patients implanted bilaterally, both eyes can be entered into the study database if they both meet eligibility criteria. Data from approximately 150 eyes will be collected by retrospective review of medical charts in 5 European countries. Countries considered at time of protocol development are: Austria, Belgium, Germany, Spain and the United Kingdom. Sites will be centers with certified XEN 45 Gel Stent surgeons known to have implanted XEN 45 Gel Stent in the time period being studied.

Patients' medical charts will be extracted until the target number of eyes for the primary analysis has been reached. Site personnel will be required to complete a screening log for patients treated with XEN 45 Gel Stent on or after 1 January 2014 to identify eligible patients (see Section 9.2). For each eye selected, all retrospective data available from baseline (i.e. day when decision was made to implant XEN 45 Gel Stent) until Last Visit (i.e. date of the last follow-up visit available prior to 1 October 2018 or date on which the patient had a SSI for glaucoma, whichever occurs first) will be extracted from existing medical records. The study will not impose any separate patient visits to the site. In case key data are not available within the charts at the site, site personnel will be asked to liaise with the patients' treating ophthalmologist to request data to be made available for investigators for data entry.

A feasibility assessment will be conducted prior to the study conduct in the considered countries to assess whether targeted sites have access to complete patient records including patient's follow up after implantation of XEN 45 Gel Stent, to assess the number of eligible eyes, and to assess sites willingness to participate in the study.

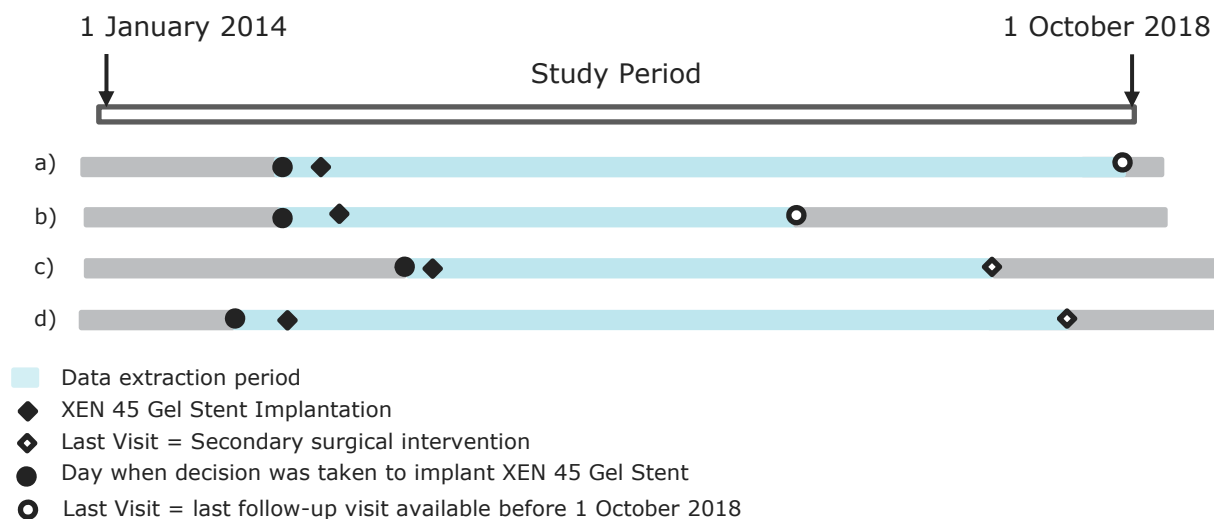
If both eyes from the same patient meet eligibility criteria, each eye will be included in the study database with a unique identifier and eyes will be paired in the electronic data capture system (EDC). Study procedures, and evaluations are described in detail in Sections 9 and 10 and data to be collected are summarized in Table 2: surgery data (procedure performed, XEN 45 Gel Stent and cataract related complication, anti-metabolite and/or antifibrotic therapy used), IOP level, number of topical IOP-lowering medications taken, eye examination (visual field exam, best corrected visual acuity...), interventions performed on the study eyes, IOP lowering medications, and AESIs. Safety events to be collected are described in Section 10.9.

Data extraction may begin as soon as sites are initiated. This study will collect anonymized data (i.e. no list of identifier will be kept by the sites and once data are entered in the system, investigators, study personnel and sponsor will not be able to identify patients), therefore no informed consent will be requested from patients.

7.2 Data Collection Periods

Figure 1 provides examples of data extraction periods for eligible eyes, depending on when baseline and Last Visit occurred during the study period.

Figure 1 Examples of Data Extraction Period for Eligible Eyes



In a) and b) eye did not have a secondary surgical intervention (SSI) for glaucoma and all data available between the day when decision was taken to implant XEN 45 Gel Stent and data cut-off, i.e. 1 October 2018, will be extracted. In c) and d), eyes had a SSI for glaucoma and data are extracted from the day when decision was taken to implant XEN 45 Gel Stent until the SSI.

Some data such as IOP and eye assessments (see Section 10.5 and 10.6 for additional details) will be collected if they are within time windows defined around data collections points of interest. All data available within these time windows have to be collected.

- Month 12: data between Month 9 and Month 15 after XEN 45 Gel Stent implantation
- Month 24: data between Month 21 and Month 27 after XEN 45 Gel Stent implantation
- Month 36: data between Month 33 and Month 39 after XEN 45 Gel Stent implantation
- Month 48: data between Month 45 and Month 51 after XEN 45 Gel Stent implantation

Table 2 displays the time frame during which study variables will be collected.

Table 2 Schedule of Data Collection

Data Collected	Baseline^[a]	XEN 45 Gel Stent Implantation	Study Period^[b]
Eligibility Assessment	X		
Demography	X		
Ocular and Glaucoma Medical History	X		
Surgery-related data		X	
Number of IOP-lowering medications	X		X
Visual field exam^[c]	X		X
Intraocular pressure	X		X
Best corrected visual acuity	X		X
Needling procedures			X
Secondary surgical intervention for glaucoma			X
Adverse events of special interest			X

IOP=intra-ocular pressure.

[a] Baseline is defined as the day when the decision was made to implant XEN 45 Gel Stent.

[b] The study period is defined as the period between XEN 45 Gel Stent implantation and 1 October 2018. For each eye selected, all retrospective data available from baseline until 1 October 2018 or until the date on which the patient received a SSI for glaucoma, whichever occurs first, will be extracted from existing medical records.

[c] If no visual field exam is available at baseline, a value measured up to 12 months prior to baseline is acceptable. In the event that more than one value is available in this 12-month period, the value closest to the baseline date will be used.

7.3 Patient Discontinuation, Site Termination or Study Termination

7.3.1 Withdrawal of Individual Patients Prior to Study Completion

Considering the retrospective study design, no withdrawal of individual patients prior to study end is expected.

7.3.2 Study or Study Site Termination

The Sponsor reserves the right, at any time, to discontinue selection of additional patients into the study, at any site; or to discontinue the study for administrative reasons.

8 STUDY POPULATION

8.1 Sites

Site selection will aim to recruit sites where investigators are certified XEN 45 Gel Stent surgeons and are known to have implanted XEN 45 Gel Stent in the time period being studied. A sample of ophthalmologists working in experienced glaucoma centers will thereby be selected.

8.2 Patients

The study population will include patients with one or both eyes with open angle glaucoma that underwent XEN 45 Gel Stent implantation.

8.2.1 Inclusion Criteria

A patient's eye must meet **all** of the following criteria to be eligible for participation in the study.

1. Eye treated with XEN 45 Gel Stent for open angle glaucoma as a standalone procedure or in combination with phacoemulsification
2. XEN 45 Gel Stent was implanted between 1 January 2014 and 1 October 2015

8.2.2 Exclusion Criteria

None

8.2.3 Minimum Required Dataset

Medical charts that do not include the following data will not be selected for the study. Therefore, if no data is available within the charts at the study site, before selecting the chart for inclusion in the study it must be established that certain key data from other locations will be made available for investigators for data entry.

Patient characteristics

- Age
- Gender

Intraocular Pressure

- IOP at baseline (i.e. medicated IOP) and until last visit (1 October 2018 or until the date on which the patient received a SSI for glaucoma, whichever occurs first)
- Number of topical IOP-lowering medication prescribed for the study eye at baseline and until last visit (1 October 2018 or until the date on which the patient received a SSI for glaucoma, whichever occurs first)

Secondary surgical intervention

- Date of the SSI for glaucoma, if any

9 STUDY PROCEDURES

9.1 Site Selection, Enrollment and Training

9.1.1 Sampling

Sites will be identified using Allergan field-based knowledge among sites where investigators are certified XEN 45 Gel Stent surgeons and are known to have implanted XEN 45 Gel Stent in the time period being studied. All sites identified by Allergan will be approached for participation in the study in the following countries of interest: Austria, Belgium, Germany, Spain and the United Kingdom.

A recruitment mail containing the study summary, the site qualification questionnaire and a reply coupon will be sent to all sites. If the return rate is insufficient, non-responders will be contacted by telephone to fill out the site qualification questionnaire.

Allergan or designee will qualify sites with sufficient resources (time, personnel, and facilities) to participate in the study. Sites will be required to obtain approval from the appropriate Independent Ethics Committee (IEC) as appropriate according to local laws, and will be responsible for maintaining all related documents, before enrollment of any patient into the study.

Recruitment will end once approximately 15 qualified sites have agreed to participate in the study.

9.1.2 Site Initiation

Sites will receive a study kit once all the necessary administrative procedures have been completed (confidentiality agreement, research contract agreement, curriculum vitae... where applicable).

The study kit contains the following:

- Study protocol
- Screening Log
- Electronic case report form (eCRF) user manual.

An initiation telephone call will be organized by Clinical Research Associates (CRA) to explain the protocol, data collection, and the practical aspects of the study.

In addition, designated study personnel will participate in a training program that will encourage consistency of processes and procedures at the investigative sites and ensure collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, and the EDC system. Retraining will be conducted as needed.

9.1.3 Site Monitoring

During the data-extraction period, sites will be contacted by telephone by CRAs to follow the site identification of patients, the eCRF completion and to answer any questions sites may have concerning data to be collected and the logistics of the study. Frequency of telephone calls will be site dependent and based on identified needs for each site. A close out call will be performed by CRAs at the end of the study. Site monitoring processes will be further detailed in the Site Management and Monitoring Plan.

9.2 Patient Identification and Selection Procedures

Medical charts will be screened by the investigative site personnel to identify eyes who satisfy all the inclusion and none of the exclusion criteria. The number of eyes selected at each site will be chosen based on the results of the feasibility assessment and consultations with the Sponsor. Eye selection will not be competitive and will stop when the target number of eligible eyes has been reached.

Once a site has been initiated, site personnel will be invited to complete a screening log with all patients' eyes that underwent XEN 45 Gel Stent implantation from 1 January 2014 until 31 December 2014. Data collected in the screening log, listed in Section 10.1, will help site personnel identify eligible eyes. Upon screening log completion, the sites will proceed through the patients' eyes listed in the screening log and extract data from eyes who meet all the inclusion criteria and none of the exclusion criteria. Consent from patients will not be requested; as the study is retrospective and fully anonymized, a waiver of consent will be requested from the IECs. Sites will proceed chronologically for entry of eligible eyes data in the EDC system, starting with the eligible eyes that underwent XEN 45 Gel Stent implantation the closest to 1 January 2014. Exceptions will be made when sites encounter an eye from a patient with both eyes meeting selection criteria. Once data from the first eye have been extracted, sites will extract data from the second eye, regardless of its XEN 45 Gel Stent implantation date, so that eyes can be paired in the EDC.

Once the charts of all eligible eyes listed in the screening log have been extracted for entry on the eCRF, and if the target number of eyes for the primary analysis has not been reached, site personnel will be invited to complete a new screening log with charts of patients' eyes that underwent XEN 45 Gel Stent implantation in the following 3 months (i.e. between 1 January 2015 and 31 March 2015). This process will be repeated periodically thereafter as applicable until the target number of eyes has been reached.

Sites will make sure that after data have been entered in the study database, there will be no possibility to link the data collected in the screening log or eCRF to a patient name.

10 STUDY ASSESSMENTS

10.1 Data Collected in the Screening Log

Once a site has been initiated, site personnel will be required to complete an anonymized screening log with all patients' eyes that underwent XEN 45 Gel Stent implantation as described in Section 9.2. If both eyes of a patient had undergone XEN 45 Gel Stent implantation, one line should be completed in the screening log per treated eye. For all screened patients' eyes, the data listed in Table 3 will be collected to help site personnel identify eligible eyes.

Table 3 Data Collected in Screening Logs

Data Collected	Selection Criteria
• Eye in which XEN 45 Gel Stent was implanted (OD vs. OS)	N/A
• Indication for XEN 45 Gel Stent implantation	IC1
• Date (MM YYYY) of XEN 45 Gel Stent implantation	IC2
• Date (MM YYYY) of Last Visit ^[a,b]	IC2
• Reason why the patient has not been selected for the study (did not meet selection criteria, lack of time, quotas were met, insufficient access to complete medical records, etc.)	N/A

IC=Inclusion criteria; N/A=not applicable; OD=oculus dexter; OS=oculus sinister

[a]. Last Visit is defined as the date of the last follow-up visit available prior to 1 October 2018 or date on which the patient had a SSI for glaucoma, whichever occurs first.

[b] Automated calculation will be implemented in the screening log to verify whether Last Visit occurred at least 3 years after XEN 45 Gel Stent implantation

10.2 Demographics

Patients' age at implantation of XEN 45 Gel Stent, gender and race will be recorded in the eCRF.

Selected eye characteristics (OD vs. OS), along with information about whether patient's other eye was also selected will be collected.

10.3 Ocular and Glaucoma Medical History

Ocular history of the selected eye will be collected, such as glaucoma diagnosis, previous ocular and glaucoma procedures, previous ocular medications (including whether or not eye is treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent) and ocular pathologies observed at baseline. Glaucoma stage at baseline will be determined by investigators based on visual field assessment.

10.4 Surgery-Related Data

Use of anti-metabolite and/or anti-fibrotic, procedure performed (i.e., XEN 45 Gel Stent implantation alone or phacoemulsification + XEN 45 Gel Stent implantation), XEN 45 Gel Stent and cataract-related complications, and, if available surgical, notes will be collected.

10.5 Intraocular Pressure Data

IOP-related data, i.e. IOP and number of IOP-lowering medications, will be collected at the visit when the decision was made to implant XEN 45 Gel Stent, and not the day of implantation. IOP-related data will also be collected for all data collection points defined for the study period.

10.6 Eye Assessments

10.6.1 Visual Field Exam

Mean deviation expressed in decibels will be collected at baseline and at all data collection points defined for the study.

Note: If no visual field exam is available at baseline, a value measured up to 12 months prior to baseline is acceptable. In the event that more than one value is available in this 12-month period, the value closest to the baseline date will be used.

10.6.2 Best Corrected Visual Acuity

BCVA in the study eye will be collected at baseline and at all data collection points defined for the study. Values will be recorded in the eCRF according to local practice (Snellen, LogMAR, EDTRS, etc.) along with scale name or method used to assess BCVA.

10.7 Needling Procedures

Date of needling procedures performed on the bleb after XEN 45 Gel Stent implantation will be collected throughout the study period.

10.8 Secondary Surgical Intervention

If a SSI for glaucoma was performed on the study eye during the study period, the nature and date of the SSI will be collected. SSIs for glaucoma include but are not limited to trabeculectomy, tube shunt, second gel stent, i-Stent, GATT, ABiC, and transscleral cycloablative procedures.

10.9 Safety Assessments

10.9.1 Definitions

The investigators will classify the adverse event based on the following definitions according to ISO 14155 (2011).

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Serious Adverse Event (SAE)

An adverse event that:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
 - 1) a life-threatening illness or injury, or

- 2) a permanent impairment of a body structure or a body function, or
 - 3) in-patient or prolonged hospitalization, or
 - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to fetal distress, fetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a serious adverse event.

Device Malfunction/Failure – Device Specific Events

A device specific event is any malfunction of the device, related or not to the device, resulting or not in the patient undergoing undesirable or harmful experience, that occurs in relation with the conduct of the study.

Device malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Device malfunction may or may not result in the subject experiencing a harmful effect.

All AEs/SAEs associated with a device failure are by definition device related.

10.9.2 Collection and reporting of Safety Events by Investigators

Considering that study aims to explore occurrence over the long term of adverse events identified during clinical studies, this study will collect only the following AESIs:

- Anterior chamber defects:
 - Shallow with peripheral iridocorneal touch
 - Flat with irido-corneal touch extending to the pupil
- Bleb leak
- Blebitis
- Choroidal effusion, hemorrhage or mixed effusion hemorrhage recorded as follows:
 - Extending posterior to the equator, without blood
 - Extending posterior to the equator, with blood
 - Obscuring disc or macula, without blood
 - Obscuring disc or macula, with blood
 - With choroids touching in the center of the eye, without blood
 - With choroids touching in the center of the eye, with blood
- Corneal decompensation (transient i.e. <30 days or persistent i.e. >30days)
- Endophthalmitis
- Hyphema

- ≥ 2 mm in height (layered) at any time
- Present or arising > 30 days postoperatively
- Persistent hypotony: IOP < 6 mmHg, present at two consecutive visits postoperatively > 30 days apart
- Clinical hypotony: vision reduction (2 lines or more) related to macular changes consistent with hypotony maculopathy (macular folds), optic disc edema, and/or serious choroidal detachments because of low IOP
- Implant blockage
- Implant exposure or extrusion / conjunctival erosion
- Implant migration
- Implant repositioning requiring surgical intervention
- Implant touching iris or cornea
- Iritis (requiring treatment after the postoperative medication taper)
- Macular edema
-
- Retinal detachment
- Suture abscess or other local infection
- Vitreous hemorrhage
- Any other adverse event that leads to permanent visual impairment or requires surgical or medical intervention to prevent permanent visual impairment

Due to the retrospective design of the study, the reporting of safety events to the sponsor is not solicited for this study. AEs occurring outside of the data collection period 01 January 2014 to 01 October 2018 are not within the scope of this study and will not be collected. However, should any AEs occur that are outside of this range, Investigators are reminded of the requirement for unsolicited AE reports to be submitted directly to Allergan's Product Surveillance.

10.9.3 Case Processing and Submission to Competent Authorities

As the study is retrospective, all AEs collected during the study should have been reported to the competent authorities at time of occurrence. AEs collected during this study will not be submitted to the competent authorities as this would result in double reporting. However, all AESIs collected for the study will be recorded in the study database and summarized in the study report.

The investigators are responsible for maintaining compliance with any applicable site-specific requirements related to the reporting of SAEs or other safety information to the local IEC that approved the study.

11 DATA SOURCES

This is a retrospective, observational study, and patient data collected from the sites will be extracted from medical charts.

12 DATA MANAGEMENT

Electronic data collection will be performed using eCRFs. Site personnel will enter data into the EDC system according to the schedule of assessments and according to instructions from the Sponsor and/or designee. Only authorized personnel will have access to the EDC system. Selected eyes will be identified by an identification number assigned when they are selected for the study. For patients implanted bilaterally, both eyes can be entered into the study database if they both eyes meet eligibility criteria. In that case, each eye will be included in the study database with a unique identifier, and eyes will be paired in the EDC. Data will be anonymized and once entered in the system, investigators and study personnel will not be able to identify patients.

Each investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner. Specific processes used to manage the data throughout the study will be documented in the Data Management Plan. Briefly, on-line logic checks will be built into the system, so that missing or illogical data are not submitted. In the event that inconsistent data persist, no queries will be issued as investigators will not be able to connect the patient with his/her eye identification number. Consequently, all data entered into the eCRF should be reviewed by the principal investigator. The principal investigator will be responsible for endorsing data within the eCRF. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, the most recent version); coding will be done at the Lower Level Term. IOP lowering medications will be coded with the WHO Drug Dictionary.

A final validation of the database will be performed, and the database will be locked, before the statistical analysis is conducted.

13 QUALITY CONTROL

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative site and ensure collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, and the EDC. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting AESI, SAEs, and other information.

Quality controls performed during statistical analyses will be described in the statistical analysis plan (SAP).

Secure electronic archive will be maintained and will include but will not be limited to: final raw data, analysis datasets, programs and associated documentation. Access to the archive will be controlled and limited to authorized personnel only.

14 STATISTICAL METHODS

14.1 Sample Size

To answer study primary objective, this chart review study plans to accrue a minimum of 60 study eyes that have had at least 3 years of follow-up data without a SSI for glaucoma after the initial implant with XEN 45 Gel Stent.

Data from the Allergan study MS-001 demonstrated that the mean IOP reduction from baseline differed slightly among the 7 visits (see below) in the 24-month post-implant period. The absence of a clear waning-out trend suggests that the effect of XEN 45 Gel Stent implantation on IOP reduction may last to Month 36 and beyond. The minimum mean reduction (negative sign stands for reduction) in IOP among the visits was -5.6 (± 6.32) mmHg, which was observed at Month 3. This value was then taken as an initial estimate for the mean reduction projected for Month 36. The 95% confidence interval (CI) of the projected mean reduction afforded by a sample of 60 study eyes is -7.2 to -4.0 mmHg. That is, the half-length of the interval is 1.6 mmHg, which provides a reasonable precision for the estimate of the projected mean reduction in IOP.

Table 4 Result from the MS-001 Study

Visit	Number of study eyes	Mean (SD) change in IOP from medicated baseline (mmHg)
Month 1	167	-6.3 (6.41)
Month 3	167	-5.6 (6.32)
Month 6	168	-6.4 (4.92)
Month 9	134	-6.1 (5.68)
Month 12	161	-6.7 (5.41)
Month 18	149	-7.1 (5.10)
Month 24	149	-6.2 (4.94)

The MS-001 study enrolled 199 patients (218 study eyes). In this study, patients' discontinuation rate tended to be linear over the 2-year follow-up period, with an overall study discontinuation rate of approximately 20%. Using data from the MS-001 study, it could be assumed that 30% of the eyes selected for this study have less than 3 years of follow-up data. Taking into consideration that MS-001 study was a clinical trial and that patient retention rate is expected to be lower in a real-world setting, the study will aim to select 150 eyes to ensure obtaining a minimum of 60 eyes with at least 3 years of follow-up data.

14.2 Study Populations and Analyses

A formal SAP that will provide details of all analyses and presentation of study data will be approved prior to data analysis. Statistical analysis will be carried out using SAS software version 9.2 or later.

14.2.1 Study Populations and Analysis Methods

- Analysis Population: all eyes selected and meeting the selection criteria.
- Subgroups analyses will be conducted in eyes that did or did not undergo phacoemulsification. Additional subgroups may be further considered in the SAP.

Continuous variables will be described by their mean, standard deviation, median, upper and lower quartiles, extreme values (minimum and maximum) and the number of missing data.

Categorical variables will be described by the number and percentage of each response and the number of missing data.

Figures will be generated, when appropriate, to describe change in parameters over time.

Some of the data will only be collected if they occurred within study-defined time windows (see Section 7.2). Since all data within the defined time windows will be collected, more than one value could be available per time window for a given parameter. Rules to determine which value will be used for the analysis will be defined in the SAP.

14.2.2 Disposition and Patients' characteristics

Number and percentage of eyes in the Analysis Population and in subgroups will be described. Demographic characteristics will be summarized descriptively at a patient level.

14.2.3 Disease Progression

Ocular medical history, IOP lowering medications and needling procedures will be summarized descriptively. Visual field exam and BCVA will be summarized descriptively at baseline and for all time points of interest.

14.2.4 Primary Objective

Change in IOP from medicated baseline and change in the number of topical IOP-lowering medications compared to baseline will be summarized descriptively at Year 3 after XEN 45 Gel Stent implantation in eyes from the Analysis Population with at least 3 years of follow-up data and were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.

14.2.5 Secondary Objectives

14.2.5.1 Change in IOP and Number of Topical IOP-Lowering Medications 4 Years after XEN 45 Gel Stent Implantation

Change in IOP from medicated baseline and change in the number of topical IOP-lowering medications compared to baseline will be summarized descriptively at Year 4 after XEN 45 Gel Stent implantation in eyes from the Analysis Population with at least 4 years of follow-up data and were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.

14.2.5.2 Success over the Long Term of following implantation of the XEN 45 Gel Stent

Number and proportion of eyes achieving a 20% reduction in IOP from medicated baseline, and number and proportion of eyes with an IOP <18 mmHg, IOP <17 mmHg, ..., down to IOP <12 mmHg will be described at all time-points of interest in eyes from the Analysis Population that did not underwent SSI for glaucoma, did not have clinical hypotony, and were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.

The number and proportion of eyes achieving qualified or complete success at 3 and 4 years after XEN 45 Gel Stent implantation will be summarized descriptively. Analyses will be conducted in the Analysis Population. Kaplan-Meier analyses will be conducted to analyze time from initial procedure to SSI for glaucoma.

14.2.5.3 Safety over the long term following implantation of the XEN 45 Gel Stent

Surgical complications and post-operative AESIs will be summarized descriptively using frequencies and percentages. Analyses will be performed in the Analysis Population.

14.3 Bias and Limitations of the Study

14.3.1 Sites

Sites will be selected to be representative of sites experienced with glaucoma management. Because the participating sites comprise a population of volunteers, a non-response selection bias is possible.

14.3.2 Patients

In order to limit bias in the selection of patients' eyes, each site will be asked to select in a chronological order all eyes that meet the selection criteria, regardless of demography or other considerations, based on date of XEN 45 Gel Stent implantation (see Section 9.2). Exception to the selection in a chronological order will be made for patients with both eyes meeting the selection criteria with both eyes included at the same time. All patients' eyes that had XEN 45 Gel Stent implanted and meeting the selection criteria, regardless of whether or not they will be selected for the study, will be recorded in an anonymized screening log collecting minimum non-identifying patient information (see Section 10.1). Characteristics of selected and non-selected patients' eyes will be compared to assess selection bias and reason for not being selected will be described (eye did not meet selection criteria, lack of time, quotas were met, site was unable to retrieve data missing from the chart from other locations etc.).

14.3.3 Information Bias

As the study is retrospective, the study will rely on data collected for another purpose (e.g. patient care). As a result, not all data to be collected in this study may be recorded in the medical charts, leading to a potential bias due to missing data.

Moreover, as data are anonymized, no queries will be issued to the sites in case of missing or incoherent data.

Finally, as this is a multicenter study conducted in different countries, the quality and quantity of medical information available from medical records will be variable. Medical records from some providers may not contain information for all encounters with the ophthalmologist. To limit this bias, it will be verified during the feasibility assessment that targeted sites have access to complete patient records, including patients' follow up after implantation. In case key data are missing from the charts at the site, site personnel will be asked to liaise with the patients' treating ophthalmologist to request data to be made available for investigators for data entry. Finally the methods used to estimate the data variables collected (e.g. visual field, best corrected visual acuity...) during the chart review process may be heterogeneous across sites. This could potentially result in greater variability in the study result.

Information bias can be minimized by the use of electronic data capture technology. In addition to minimize the burden on the investigators and the sites, electronic data capture technology will maximize the quality and relevance of the data using automated online controls (e.g., automated controls on value ranges, units, internal consistency, and missing key data).

15 ETHICAL CONDUCT OF THE STUDY

15.1 Ethics Statement

To ensure the quality and integrity of research, the study shall be conducted in compliance with the ethical principles arising from the Declaration of Helsinki revised in 2013 (World Medical Association, 2013), ISO-14155-2011 (ISO, 2011), the MEDDEV 2.12/2 rev2 (MEDDEV, 2012), European and National laws in terms of data protection and all current local regulations (2016/679, 2016).

15.2 Informed Consent

Due to the retrospective and anonymous nature of data collection for this study, signature of informed consent by patients is not required to extract data from the patient's chart. A waiver of consent will be requested from IECs.

15.3 Institutional Review Board / Independent Ethics Committee Approval

This study is non-interventional. As the study is based on a secondary use of data, it does not come under applicable laws and regulation on clinical trials

Submissions and/or notification to the appropriate IEC will be performed as required by local legislation in each country for this type of study.

Patients' personal data and investigator's personal data shall be treated in compliance with the European Regulation (EU 2016/679) on the protection of individuals with regard to the processing of personal data and all local applicable laws and regulations.

Data about investigators will be declared to applicable data protection authority and the investigators will be informed – within the framework of the site qualification questionnaire – of their right to access to, rectify or erase data, or their right to restrict or object to processing of the data, as well as the right to data portability.

Patient data will be anonymized, i.e. investigators will not be able to connect the patient with his/her identification number. The sponsor will be blinded to the patient information.

Submission(s) to competent data protection authorities will be performed as appropriate.

15.4 Adherence to the Protocol

The study must be conducted as described in the approved protocol. Any significant deviation from the protocol (i.e. jeopardizing patient safety) must be reported immediately to the Sponsor and IEC.

15.5 Protocol Amendment

Any amendment to the protocol will be created by the Sponsor, and subsequently submitted by the site to the IEC and appropriate regulatory authority for approval.

15.6 Retention of Patient Records

When the study is completed, the investigators must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The investigators will notify the Sponsor prior to moving or destroying any of the study documents.

The Sponsor will maintain the data collected (study database) for at least 5 years.

15.7 Confidentiality

The information in this and related documents from the Study Sponsor includes trade secrets and commercial information that are confidential and may not be disclosed, unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted below, is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare.

Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IEC, or local regulatory agency.

16 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY REPORT

The Sponsor and/or designee will develop a final study report after the end of the study. Results will be posted on Clinical Trials.gov.

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. . Authorship credit will follow the guidelines established by the International Committee of Medical Journals Editors (ICMJE, 2016) and, as such, should be based on the following criteria 1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; 2) drafting the work or revising it critically for important intellectual content; 3) final approval of the version to be published and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors must meet all above criteria. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above.

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APPENDICES

None